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In the Supreme Court of the United States

OCTOBER TERM, 1964.

No. 701.

DR. HENRY TURKEL and UBIOTICA CORPORATION,

Petitioners,

v.

FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH, EDUCATION AND WELFARE,

Respondent.

PETITION FOR A WRIT OF CERTIORARI
To the United States Court of Appeals
For the Sixth Circuit.

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DEPARTMENT OF HEALTH, EDUCATION AND WELFARE,

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PETITION FOR A WRIT OF CERTIORARI
To the United States Court of Appeals
For the Sixth Circuit.

Petitioners pray that a Writ of Certiorari issue to review the judgment of the United States Court of Appeals for the Sixth Circuit entered in the above case on July 21, 1964.

OPINION BELOW.

The opinion of the Court of Appeals for the Sixth Circuit is reported at 334 F. 2d 844; and is printed in the Appendix hereto, *infra*, pp. 12-16.

JURISDICTION.

The judgment of the Court of Appeals was entered on July 21, 1964 (page 17, *infra*). Rehearing was denied on September 14, 1964 (page 18, *infra*). The jurisdiction of this Court is invoked under 28 U. S. C., Section 1254(1).

QUESTIONS PRESENTED.

In a suit filed under the provisions of 21 U. S. C. 355-(h), providing for a Petition to Review an order withdrawing approval of an application granting an exemption for the investigational use of a drug, the Court of Appeals for the Sixth Circuit granted the Respondent's Motion to Dismiss said Petition to Review. The Court of Appeals stated in its decision that there was no recourse available to the Petitioners to review the order of the Food and Drug Administration, issued against the Petitioners. The Court of Appeals further made a finding that a tendered record of the Food and Drug Administration could not be received by the Court for its consideration in connection with the issues presented in this cause. The questions presented are:

1. Whether the 1962 Amendments to the Food and Drug Act that the right of appeal to the United States Court of Appeals granted by 21 U. S. C., Section 355(h), applies to an order of the Secretary, Health, Education and Welfare Department, withdrawing approval of an investigational exemption granted permitting the distribution of a drug for investigational use.

2. Whether Section 262 of the Judicial Code grants jurisdiction to federal courts to review an order of the Secretary, Health, Education and Welfare Department, withdrawing approval of an investigational exemption granted permitting the distribution of a drug for investigational use.

3. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution protects against unreasonable and unwarranted conditions imposed by regulations adopted by a federal agency under a directive contained in an Act of Congress.

4. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution protects against an unreasonable and unwarranted interference in the investigational use of a drug, when all of the medical evidence available with respect to the investigational use of said drug indicates that the same is devoid of harmful effects, and beneficial to those patients being administered the same.

5. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution protects against a proceeding, where an investigational use exemption is withdrawn by the Food and Drug Administration, without a hearing, without confrontation, and without an opportunity to present evidence germane to the subject matter, before such time as a final order of the Food and Drug Administration is issued with respect to the termination of the investigational use exemption in existence.

6. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution protects duly licensed physicians against the unbridled and arbitrary use of power by the Food and Drug Administration in refusing to present and disclose reasons upon which is premised an order of termination of an existing exemption authorizing the investigational use of a drug.

7. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution requires a judicial review of proceedings conducted by a federal agency, wherein said federal agency denies a hearing, confrontation and findings before a final order is issued to Petitioners.

CONSTITUTION, STATUTES, FEDERAL RULES AND REGULATIONS INVOLVED.

Involved herein are the following: Amendment V, U. S. Constitution, set forth in the Appendix at page 18; Federal Food, Drug and Cosmetic Act, as amended, 21 U. S. C. 355, set forth in the Appendix at pp. 19-27; Regulations adopted by the Food and Drug Administration, 28 Federal Register, 170-182, 319, 5048 (21 C. F. R. 130.3), set forth in the Appendix at pages 27-48; and Rules 26 and 33 of the Federal Rules of Civil Procedure.

STATEMENT.

In 1943, Dr. Henry Turkel developed and created a certain combination of drugs and vitamins, which were then and are now commonly used as medicines, which are called the "U" Series Drugs. The purpose of the "U" Series Drugs is for the medical treatment of the condition known as mongolism, which is a recognized medical phenomenon existing in certain human beings.

Between the years 1943 and 1957, certain modifications with respect to the ingredients were made by the Petitioners; and since 1957, the ingredients have remained constant.

Since the year 1957, the "U" Series Drugs have been prescribed by the Petitioners and by many other physicians throughout the United States, and used in the treatment of hundreds of mongoloid patients, with marked results indicating that the same are a safe and effective treatment.

Prior to October, 1962, the Petitioners presented their findings to the Food and Drug Administration, and were used between 1957 and 1962 with the full knowledge of the said Food and Drug Administration.

When the existing Federal Food, Drug and Cosmetic Act was amended in October, 1962, the Petitioners there-

after filed a "Notice of Claimed Investigational Exemption for New Drug" pursuant to the provisions of the statute and certain regulations adopted by the Food and Drug Administration. On October 4, 1963, Petitioners received a notice from the Food and Drug Administration raising certain questions relative to the manufacture, composition, processing and animal testing of the "U" Series Drugs. On October 10, 1963, the information requested was furnished by the Petitioners, with the exception of technical data which was in the process of preparation by Direct Laboratories, Inc., Buffalo, New York, a pharmaceutical manufacturer licensed, supervised and inspected by the Food and Drug Administration.

On November 29, 1963, the Food and Drug Administration issued an order terminating the investigational use exemption, and decreeing that the Petitioners discontinue the administration of the "U" Series Drugs to human beings.

Upon receip of this order of the Food and Drug Administration, the Petitioners requested a hearing, which was held on December 17, 1963, at which hearing the Petitioners were denied the right to learn of the basis of the findings, or of the findings themself, of the Food and Drug Administration; Petitioners were further denied the right to interrogate the personnel of the Food and Drug Administration; further Petitioners were denied the right of apprisal of the basis of the issuance of the order by the Food and Drug Administration.

As a result of the issuance of the order by the Food and Drug Administration, in excess of 100 patients who were receiving the "U" Series Drugs as a medical treatment were denied the same, which action resulted in, and continues to result in regression of their physical condition.

The Food and Drug Administration further notified the Petitioners that if the order of November 29, 1963, was violated, that Petitioners would be prosecuted criminally.

The Food and Drug Administration refused and failed to answer requests by the Petitioners for further proceedings; and in effect, became incommunicado to the Petitioners' request for a formal hearing or for other proceedings with respect to the order of November 29, 1963.

Under and by virtue of the provisions of 21 U. S. C., Section 355(h), the Petitioners instituted a Petition to Review in the U. S. Court of Appeals for the Sixth Circuit.

Under the provisions of 21 U. S. C., Section 355(h), the Respondent, the Food and Drug Administration, tendered to the Court of Appeals the record, requesting that the same be filed "in camera" with the Court. The Court of Appeals refused to file the same, and hence at no time was the complete record before the Court of Appeals.

A Motion to Dismiss was filed by the Food and Drug Administration, which Motion was granted by the Court of Appeals, based upon their interpretation of the provisions of 21 U. S. C., Section 355(h). This interpretation stated in essence that the Petitioners have no regress or recourse from the action of the Food and Drug Administration; and further that the Due Process Clause of the Fifth Amendment has not been violated by the summary and arbitrary action of the Food and Drug Administration.

The Court of Appeals in its decision, by way of dictum, interprets the provisions of the statute and the regulations adopted pursuant thereto in such a manner as would suggest that the facts of this case were not before the Court.

The Court of Appeals in the oral argument on the Motion to Dismiss, asked the question: "Is there any protection afforded to the Petitioners in the event that the

Commissioner of the Food and Drug Administration exercises the power granted to him by the statute and the regulations in a dishonest manner?"

While the answer to this question was discussed in oral argument before the Court of Appeals, the Court completely ignored the same in its opinion and decision.

In effect, the Court held that there was no protection to the Petitioners in this case where all of the procedural requirements of due process were ignored and denied to the Petitioners by the arbitrary, unwarranted and summary action of the Food and Drug Administration.

REASONS FOR GRANTING THE WRIT.

The decision below should be reviewed because it erroneously interprets the 1962 Amendments to the Federal Food, Drug and Cosmetic Act, so as to deny the Petitioners the right of judicial review of a final order of the Food and Drug Administration.

1. This cause presents a public question high in the scale of the nation's interest in public health, and presents a compelling justification for prompt judicial resolution of the controversy over the power of the Food and Drug Administration to determine whether research and investigational use of a drug can be carried on by a physician. The issue here is whether a judicial review is available to the Petitioners, in a case where the sole interest and efforts of the Petitioners are directed toward an improvement of the public health of certain of its citizens.

The sole purpose of the Petitioners is to seek judicial review of an order of the Food and Drug Administration, which Petitioners contend was made in excess of the delegated powers of the Food and Drug Administration.

Accordingly, as this Court stated in the case of *Boire v. Greyhound Corporation*, 376 U. S. 473, where a public question is high in the scale of our national interest, there is justification for a prompt judicial review of said question. This Court followed the tenor of its pronouncement made previously in the case of *Leedom v. Kyne*, 358 U. S. 184.

2. The Court below sought to avoid the questions raised by the Petition to Review, by summarily assuming, without reference to the record in this cause, that the order of the Food and Drug Administration was not a "final order." No such assumption is justified by the record herein.

However, when the Food and Drug Administration filed the record required by the provisions of 21 U. S. C. 355(h), and attempted to place a reservation to the examination by the Court of these records, by requesting that they be filed "in camera," the Court below refused to look at the record and consider the same in the determination of whether their assumption was correct or incorrect.

Accordingly, the Court below made a determination with respect to jurisdiction by a narrow and unrealistic finding that the pertinent provisions of the statute did not apply to the facts in this case; when in truth and fact, the Court did not apprise itself of the record tendered for filing by the Food and Drug Administration; and ignored by the Court completely in this case.

3. In the interpretation of 21 U. S. C. 355(h), and other pertinent sections of the Federal Food, Drug and Cosmetic Act, the Court did not consider the obliteration of the right of the Petitioners to engage in the investigational use of a drug.

Nor did the Court consider that such interpretation of the statute was a denial of the Due Process Clause of the Fifth Amendment.

However, this Court in the case of *Leedom v. Kyne*, 358 U. S. 184, has stated at page 190 as follows:

> "Here * * * absence of jurisdiction of the federal courts would mean a sacrifice or obliteration of a right which Congress has given professional employees for there is no other means, within their control to protect and enforce that right. And 'the inference is strong that Congress intended the statutory provisions governing the general jurisdiction of those courts to control.' * * * This Court cannot lightly infer that Congress does not intend judicial protection of rights it confers against agency action taken in excess of delegated powers. Cf. *Harmon v. Brucker*, 355 U. S. 579; *Stork v. Wickard*, 321 U. S. 288; *School of Magnetic Healing v. McAnnulty*, 187 U. S. 94."

4. In the interpretation of the Federal Food, Drug and Cosmetic Act made by the Court below, the Court was not mindful of the pronouncement of this Court in the case of *American Federation of Labor v. National Labor Relations Board*, 308 U. S. 401, p. 408, where it is stated as follows:

> "* * * Administrative determinations which are not commands may for all practical purposes determine rights as effectively as a judgment of a Court, and may be re-examined by Courts under particular statutes providing for review of 'orders.' See *Rochester Telephone Corp. v. United States*, 307 U. S. 125, 130, 135, et seq.; *Federal Power Comm'n. v. Pacific Power & Light Co.*, 307 U. S. 156."

5. The Court below in its interpretation of the Federal Food, Drug and Cosmetic Act, and the Regu-

lations adopted pursuant thereto, did not consider the denial of the guarantees of the Due Process requirements of the Fifth Amendment of the U. S. Constitution.

The record shows that the procedures followed by the Food and Drug Administration in terminating the exemption violated the traditional concepts of Due Process, in that a finding was made without an opportunity to be heard, and a proceeding had in which no applicable rules of law and procedures were observed or allowed; all in direct contravention of the statements of this Court in the cases of *St. Joseph Stock Yards Co. v. United States,* 298 U. S. 38; *Rochin v. California,* 342 U. S. 165; *Yanataya v. Fisher,* 189 U. S. 86.

As this Court has stated and reaffirmed, the individual's substantial rights must be protected, where the Government is exercising the power to regulate, license and control an entire branch of business. *Cafeteria & Restaurant Workers Union, Local 473, AFL-CIO v. McElroy,* 367 U. S. 886.

The questions presented by this case are of great and recurring significance in the administration of the 1962 Amendments to the Federal Food, Drug and Cosmetic Act, and elsewhere. The serious question of the denial of the right of judicial review, and the effect of the decision below, if unreversed, on the unbridled power and authority of a federal agency, makes this case a peculiarly appropriate one for the exercise of this Court's discretionary jurisdiction.

CONCLUSION.

For the reasons set forth above, it is respectfully submitted that this Petition for a Writ of Certiorari should be granted.

LEO E. RATTAY,
Counsel for Petitioners.

APPENDIX.

OPINION OF THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT.

(Decided July 21, 1964.)

Before: MILLER, PHILLIPS and EDWARDS, Circuit Judges.

EDWARDS, Circuit Judge. Respondent, Food and Drug Administration, filed a motion to dismiss the appeal which petitioners, Dr. Henry Turkel and Ubiotica Corporation, initially filed in this court under Section 505(h) of the Federal Food, Drug and Cosmetic Act, 21 U. S. C. § 355-(h).

The petition sought to enjoin and vacate an order of the Commissioner of Food and Drugs terminating the investigational exemption previously allowed petitioners for investigational distribution of the "U" Series Drugs in the treatment of mongolism in children.

The motion to dismiss was based on the contention that Section 505(h) of the Act, 21 U. S. C. § 355, which grants a right of appeal to the United States Court of Appeals "for the circuit wherein such applicant resides or has his principal place of business" is not applicable "since there has been no order refusing to approve a new drug application." In view of the fact that the petition called for determination of a matter of first impression, this court set the motion to dismiss for oral argument.

The legislation under which the order complained of was issued is a direct product of the disclosure that the drug thalidomide had been responsible for the birth of many malformed infants in countries where it had been widely administered to pregnant women. Subsequent to these tragic events, Congress enacted amendments to the Food and Drug Act greatly widening the powers of the

Secretary to adopt regulations pertaining to interstate distribution and sale of new drugs. The new amendments also authorized promulgation of regulations for exempting from the new drug application requirements drugs intended solely for investigational use by experts. 21 U. S. C. § 355, as amended October 10, 1962. Public Laws 87-781, § 103(b), 76 Stat. 783, 21 U. S. C. § 355(i).

Among the important provisions of the 1962 Amendments were provisions which placed upon the applicant the burden of establishing that the drug proposed to be distributed in interstate commerce was safe for human use, and requiring testing prior to approval of such new drug application, with the power extended to the Secretary to require tests on animals.

Petitioners had been manufacturing the "U" Series Drugs and testing them on Mongoloid children under medical supervision for some eleven years prior to the adoption of the 1962 Amendments. On June 5, 1963, they filed "Notice of Claimed Investigational Exemption for a New Drug" under 21 U. S. C. § 355(i), as amended October 10, 1962.

On September 30 the Commissioner of Food and Drugs wrote petitioners notifying them of "inadequacies" in their "Notice of Claimed Investigational Exemption" for the "U" Series Drugs. Among other asserted deficiencies there were these entries: "No animal data are submitted. There is an inadequate amount of reporting of clinical data. * * * No real plan is submitted." The letter required correction of the inadequacies within ten days of receipt.

This was followed on November 26 by a letter from the Commissioner to petitioners notifying them: "The conditions of exemption have not been met, and the exemption allowing clinical testing of the drug is terminated. You

should immediately recall the drug from all clinical investigators and discontinue administering it to human beings."

Subsequent thereto an informal conference was held in the office of the Assistant Commissioner, Winton B. Rankin, on Tuesday, December 17, 1963, between representatives of the Food and Drug Administration and the petitioners at which the controversy was reviewed at some length. At this conference the position of the Commissioner was reaffirmed by the representatives of the Food and Drug Administration who were present. Petitioners thereupon filed a petition in this court to review the decision of the Food and Drug Administration terminating the investigational exemption as conveyed in the Commissioner's letter of November 26, 1963.

Prior to initiation of this petition for review, petitioners had also filed and then withdrawn a New Drug Application.

Respondent Food and Drug Administration moved to dismiss this appeal on the ground that 21 U. S. C. § 355-(h), relied upon by petitioners as establishing their right of appeal to this court, did not in fact confer jurisdiction upon this court in relation to withdrawal of an exemption for investigational distribution of a drug. Respondent asserts that said section grants a right to appeal only from an order of the Food and Drug Administration approving or disapproving a New Drug Application.

After briefing of the question involved and oral argument thereon, this court has concluded that the government's motion to dismiss should be granted. It is our interpretation of the 1962 Amendments to the Food and Drug Act that the right of appeal to the United States Court of Appeals granted by 21 U. S. C. § 355(h) applies only to an order of the Secretary refusing or withdrawing

approval of an application for sale and distribution of a new drug. The denial of investigational exemption does not prohibit the processing of an application for distribution and sale of a new drug through the statutorily provided hearing and final administrative order called for in 21 U. S. C. § 355(b), (c), (d), (e) and (f).

Essentially, petitioners contend before us that requiring them to proceed with the New Drug Application and hearing prior to judicial review is a futile exercise, since they contend denial is a foregone conclusion. The answer to this is that by proceeding through the New Drug Application procedure and hearing, an adequate record for review will be developed in accordance with the congressional intent. The statute appears to us to contemplate appeal to the courts only after exhaustion of the administrative remedies and entry of a final administrative order.

This interpretation is strengthened by the fact that subsection (h) upon which petitioners rely is placed immediately following the subsections dealing with applications for distribution of new drugs, and immediately prior to the section providing for exemptions of drugs for research.

As bearing on congressional intent in this regard, we also note that the first sentence of subsection (i) pertains to "Exemption of drugs for research" and reads as follows:

> "The Secretary shall promulgate regulations for exempting *from the operation of the foregoing subsections of this section* drugs intended solely for investigational use by experts * * *." (Emphasis added) 21 U. S. C. § 355(i).

Subsection (h), which contains the appeal procedure, is one of the "foregoing subsections."

As bearing on the questions posed by this appeal, we also note that the Food and Drug Administration has promulgated regulations granting a prompt hearing in the

event the applicant desires to protest a rejection by them of his New Drug Application as inadequate or incomplete.

"§ 130.5 Reasons for refusing to file applications.

"(d) if an applicant disputes the finding that his application is incomplete or inadequate, he may make written request to file the application over protest. In such case, the application shall be reevaluated, and within 30 days of the date of receipt of such written request, the application shall be approved, or the applicant shall be given written notice of an opportunity for a hearing on the question whether the application is approvable." 21 C. F. R., Section 130.5(d), as revised June 20, 1963, 28 F. R. 6380.

In the event a petitioner's New Drug Application is rejected on grounds of inadequacy of human investigational data, where an investigational exemption had previously been refused, it appears that the merits of such refusal could be a proper issue at the New Drug Application hearing and thus be preserved for appellate review.

Such an interpretation of the statute and regulations appears to us also to be strongly suggested by the due process requirements of the Fifth Amendment.

We conclude that the statute upon which petitioner relies does not grant a right of appeal from withdrawal of an investigational exemption, except by appeal from subsequent denial of a New Drug Application.

The jurisdiction of the United States Courts of Appeal to review administrative acts of federal agencies is wholly dependent upon statute. *American Federation of Labor v. National Labor Relations Board*, 308 U. S. 401 (1940); *United States v. Agne*, 161 F. 2d 331 (C. A. 3, 1947).

The petition for review is dismissed.

JUDGMENT OF THE COURT OF APPEALS

(Filed July 21, 1964.)

Before: MILLER, PHILLIPS and EDWARDS, Circuit Judges.

This court having received in the above-styled matter certain documents tendered by respondent, Food and Drug Administration, for filing as the record on appeal, along with a letter from counsel for respondent claiming executive privilege in relation to said documents and requesting that the court consider them *in camera;* and

This court having instructed the Clerk of the court not to file these documents as the record on appeal under the conditions under which they were tendered; and

This petition for review having now been dismissed on motion for want of jurisdiction in this court, without court inspections of or consideration of the documents referred to,

NOW, THEREFORE, the Clerk of the United States Court of Appeals is directed forthwith to return said documents to counsel for respondent.

Approved for entry,

GEORGE EDWARDS,
Circuit Judge.

ORDER OF COURT OF APPEALS DENYING PETITION FOR REHEARING EN BANC.

(Filed September 14, 1964.)

BEFORE: WEICK, Chief Judge; MILLER, CECIL, O'SULLIVAN, PHILLIPS and EDWARDS, Circuit Judges.

The petition for rehearing en banc is hereby denied, and it is ordered that the petition for rehearing be referred to the panel of judges which heard the case.

Approved for entry,

GEORGE EDWARDS,
Circuit Judge.

ORDER OF COURT OF APPEALS DENYING PETITION FOR REHEARING.

(Filed September 14, 1964.)

BEFORE: MILLER, PHILLIPS and EDWARDS, Circuit Judges.

The petition for rehearing is hereby denied.

Approved for entry,

GEORGE EDWARDS,
Circuit Judge.

THE CONSTITUTIONAL AMENDMENT INVOLVED.

Amendment V.

No person shall * * * be deprived of life, liberty, or property, without due process of law * * *.

STATUTES AND REGULATIONS.

Federal Food, Drug, and Cosmetic Act, 21 U. S. C. 301, et seq.

21 U. S. C. 355.

(a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug.

(b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is ap-

provable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

(d) If the Secretary finds, after due notice to the applicant in accordance with subsection (c) and giving him an opportunity for a hearing, in accordance with said subsection, that (1) the investigations, reports of which are required to be submitted to the Secretary pursuant to subsection (b), do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling thereof; (2) the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions; (3) the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; (4) upon the basis of the information submitted to him as part of the application, or upon the basis of any other information before him with respect to such drug, he has insufficient information to determine whether such drug is safe for use under such conditions; or (5) evaluated on the basis of the information submitted to him as part of the application and any other information before him with respect to such drug, there is a lack of substantial evidence that the drug will have the effect it purports or is

represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof; or (6) based on a fair evaluation of all material facts, such labeling is false or misleading in any particular; he shall issue an order refusing to approve the application. If, after such notice and opportunity for hearing, the Secretary finds that clauses (1) through (6) do not apply, he shall issue an order approving the application. As used in this subsection and subsection (e), the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

(e) The Secretary shall, after due notice and opportunity for hearing to the applicant, withdraw approval of an application with respect to any drug under this section if the Secretary finds (1) that clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved; (2) that new evidence of clinical experience, not contained in such application or not available to the Secretary until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the Secretary when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved; or (3) on the basis of new in-

formation before him with respect to such drug, evaluated together with the evidence available to him when the application was approved, that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof; or (4) that the application contains any untrue statement of a material fact: Provided, That if the Secretary (or in his absence the officer acting as Secretary) finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately, and give the applicant prompt notice of his action and afford the applicant the opportunity for an expedited hearing under this subsection; but the authority conferred by this proviso to suspend the approval of an application shall not be delegated. The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application with respect to any drug under this section if the Secretary finds (1) that the applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports, in accordance with a regulation or order under subsection (j), or the applicant has refused to permit access to, or copying or verification of, such records as required by paragraph (2) of such subsection; or (2) that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of; or (3) that

on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. Any order under this subsection shall state the findings upon which it is based.

(f) Whenever the Secretary finds that the facts so require, he shall revoke any previous order under subsection (d) or (e) refusing, withdrawing, or suspending approval of an application and shall approve such application or reinstate such approval, as may be appropriate.

(g) Orders of the Secretary issued under this section shall be served (1) in person by any officer or employee of the Department designated by the Secretary or (2) by mailing the order by registered mail or by certified mail addressed to the applicant or respondent at his last-known address in the records of the Secretary.

(h) An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. A copy of such petition shall be forthwith transmitted by the clerk of the court to the Secretary, or any officer designated by him for that purpose, and thereupon the Secretary shall certify and file in the court the record

upon which the order complained of was entered, as provided in section 2112 of title 28, United States Code. Upon the filing of such petition such court shall have exclusive jurisdiction to affirm or set aside such order, except that until the filing of the record the Secretary may modify or set aside his order. No objection to the order of the Secretary shall be considered by the court unless such objection shall have been urged before the Secretary or unless there were reasonable grounds for failure so to do. The finding of the Secretary as to the facts, if supported by substantial evidence, shall be conclusive. If any person shall apply to the court for leave to adduce additional evidence, and shall show to the satisfaction of the court that such additional evidence is material and that there were reasonable grounds for failure to adduce such evidence in the proceeding before the Secretary, the court may order such additional evidence to be taken before the Secretary and to be adduced upon the hearing in such manner and upon such terms and conditions as to the court may seem proper. The Secretary may modify his findings as to the facts by reason of the additional evidence so taken, and he shall file with the court such modified findings which, if supported by substantial evidence, shall be conclusive, and his recommendation, if any, for the setting aside of the original order. The judgment of the court affirming or setting aside any such order of the Secretary shall be final, subject to review by the Supreme Court of the United States upon certiorari or certification as provided in section 1254 of title 28 of the United States Code. The commencement of proceedings under this subsection shall not, unless specifically ordered by the court to the contrary, operate as a stay of the Secretary's order.

(i) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections

of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(1) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(2) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator, or to clinics, for administration to human beings; and

(3) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b).

Such regulations shall provide that such exemption shall be conditioned upon the manufacturer, or the sponsor of the investigation, requiring that experts using such drugs for investigational purposes certify to such manufacturer or sponsor that they will inform any human beings to whom such drugs, or any controls used in connection therewith, are being administered, or their representatives, that such drugs are being used for investigational purposes and will obtain the consent of such human beings or their representatives, except where they deem it not feasible or, in their professional judgment, contrary to the best interests of such human beings. Nothing in this subsection shall be construed to require any clinical investigator to submit directly to the Secretary reports on the investigational use of drugs.

(j) (1) In the case of any drug for which an approval of an application filed pursuant to this section is in effect, the applicant shall establish and maintain such records, and make such reports to the Secretary, of data relating to clinical experience and other data or information, received or otherwise obtained by such applicant with respect to such drug, as the Secretary may by general regulation, or by order with respect to such application, prescribe on the basis of a finding that such records and reports are necessary in order to enable the Secretary to determine, or facilitate a determination, whether there is or may be ground for invoking subsection (e) of this section: Provided, however, That regulations and orders issued under this subsection and under subsection (i) shall have due regard for the professional ethics of the medical profession and the interests of patients and shall provide, where the Secretary deems it to be appropriate, for the examination, upon request, by the persons to whom such

regulations or orders are applicable, of similar information received or otherwise obtained by the Secretary.

(2) Every person required under this section to maintain records, and every person in charge or custody thereof, shall, upon request of an officer or employee designated by the Secretary, permit such officer or employee at all reasonable times to have access to and copy and verify such records.

28 Federal Register 170-182, 319, 5048.

21 C. F. R. 130.3.

(a) A shipment or other delivery of a new drug shall be exempt from Section 505(a) of the act if all the following conditions are met:

(1) The label of such drug bears the statement "Caution: New drug—Limited by Federal (or United States) law to investigational use."

(2) The person claiming the exemption has filed with the Food and Drug Administration a completed and signed "Notice of claimed investigational exemption for a new drug" in triplicate, with the following information:

Form FD 1571

Department of Health, Education, and Welfare, Food and Drug Administration

Notice of Claimed Investigational Exemption for a New Drug

Name of sponsor _____

Address _____

Name of investigational drug _____

To the Secretary of Health, Education, and Welfare,

For the Commissioner of Food and Drugs, Washington 25, D. C.

Dear Sir:

The sponsor, _____ submits this notice of claimed investigational exemption for a new drug under the provisions of section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 130.3 of Title 21 of the Code of Federal Regulations.

Attached hereto are:

1. The best available descriptive name of the drug, including to the extent known the chemical name and structure of any new-drug substance, and a statement of how it is to be administered. (If the drug has only a code name, enough information should be supplied to identify the drug.)

2. Complete list of components of the drug, including any reasonable alternates for inactive components.

3. Complete statement of quantitative composition of drug, including reasonable variations that may be expected during the investigational stage.

4. Description of source and preparation of any new-drug substances used as components, including the name and address of each supplier or processor, other than the sponsor, of each new-drug substance.

5. A statement of the methods, facilities, and controls used for the manufacturing, processing, and packing of the new drug to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug.

6. A statement covering all information available to the sponsor derived from preclinical investigations and any clinical studies and experience with the drug as follows:

a. Adequate information about the preclinical investigations, including studies made on laboratory animals, on the basis of which the sponsor has concluded that it is reasonably safe to initiate clinical investigations with the drug: Such information should include identification of the person who conducted each investigation; identification and qualifications of the individuals who evaluated the results and concluded that it is reasonably safe to initiate clinical investigations with the drug and a statement of where the investigations were conducted and where the records are available for inspection; and enough details about the investigations to permit scientific review. The preclinical investigations shall not be considered adequate to justify clinical testing unless they give proper attention to the conditions of the proposed clinical testing. When this information, the outline of the plan of clinical pharmacology, or any progress report on the clinical pharmacology, indicates a need for full review of the preclinical data before a clinical trial is undertaken, the Department will notify the sponsor to submit the complete preclinical data and to withhold clinical trials until the review is completed and the sponsor notified. The Food and Drug Administration will be prepared to confer with the sponsor concerning this action.

b. If the drug has been marketed commercially or investigated (e.g. outside the United States), complete information about such distribution or investigation shall be submitted, along with a complete bibliography of any publications about the drug.

c. If the drug is a combination of previously investigated or marketed drugs, an adequate summary of preexisting information from preclinical and clinical investigations and experience with its components, including all

reports available to the sponsor suggesting side-effects, contraindications, and ineffectiveness in use of such components: Such summary should include an adequate bibliography of publications about the components and may incorporate by reference any information concerning such components previously submitted by the sponsor to the Food and Drug Administration. Include a statement of the expected pharmacological effects of the combination.

7. A total of five copies of all informational material, including label and labeling, which is to be supplied to each investigator: This shall include an accurate description of the prior investigations and experience and their results pertinent to the safety and possible usefulness of the drug under the conditions of the investigation. It shall not represent that the safety or usefulness of the drug has been established for the purposes to be investigated. It shall describe all relevant hazards, contraindications, side-effects, and precautions suggested by prior investigations and experience with the drug or chemically or pharmacologically related drugs for the information of clinical investigators.

8. The scientific training and experience considered appropriate by the sponsor to qualify the investigators as suitable experts to investigate the safety of the drug, bearing in mind what is known about the pharmacological action of the drug and the phase of the investigational program that is to be undertaken.

9. The names and a summary of the training and experience of each investigator and of the individual charged with monitoring the progress of the investigation and evaluating the evidence of safety and effectiveness of the drug as it is received from the investigators, together with a statement that the sponsor has obtained from each

investigator a completed and signed form, as provided in subparagraph (12) or (13) of this paragraph, and that the investigator is qualified by scientific training and experience as an appropriate expert to undertake the phase of the investigation outlined in Section 10 of the "Notice of claimed investigational exemption for a new drug." (In crucial situations, phase 3 investigators may be added and this form supplemented by rapid communication methods, and the signed form FD 1573 shall be obtained promptly thereafter.)

10. An outline of any phase or phases of the planned investigations, as follows:

a. Clinical pharmacology. This is ordinarily divided into two phases: Phase 1 starts when the new drug is first introduced into man—only animal and in vitro data are available—with the purpose of determining human toxicity, metabolism, absorption, elimination, and other pharmacological action, preferred route of administration, and safe dosage range; phase 2 covers the initial trials on a limited number of patients for specific disease control or prophylaxis purposes. A general outline of these phases shall be submitted, identifying the investigator or investigators, the hospitals or research facilities where the clinical pharmacology will be undertaken, any expert committees or panels to be utilized, the maximum number of subjects to be involved, and the estimated duration of these early phases of investigation. Modification of the experimental design on the basis of experience gained need be reported only in the progress reports on these early phases, or in the development of the plan for the clinical trial, phase 3. The first two phases may overlap and, when indicated, may require additional animal data before these phases can be completed or phase 3 can be

undertaken. Such animal tests shall be designed to take into account the expected duration of administration of the drug to human beings, the age groups and physical status, as for example, infants, pregnant women, premenopausal women, of those human beings to whom the drug may be administered, unless this has already been done in the original animal studies.

b. Clinical trial. This phase 3 provides the assessment of the drug's safety and effectiveness and optimum dosage schedules in the diagnosis, treatment, or prophylaxis of groups of subjects involving a given disease or condition. A reasonable protocol is developed on the basis of the facts accumulated in the earlier phases, including completed and submitted animal studies. This phase is conducted by separate groups following the same protocol (with reasonable variations and alternatives permitted by the plan) to produce well-controlled clinical data. For this phase, the following data shall be submitted:

i. The names and addresses of the investigators. (Additional investigators may be added.)

ii. The specific nature of the investigations to be conducted, together with information or case report forms to show the scope and detail of the planned clinical observations and the clinical laboratory tests to be made and reported.

iii. The approximate number of subjects (a reasonable range of subjects is permissible and additions may be made), and criteria proposed for subject selection by age, sex, and condition.

iv. The estimated duration of the clinical trial and the intervals, not exceeding 1 year, at which progress reports showing the results of the investigations will be submitted to the Food and Drug Administration.

(The notice of claimed investigational exemption may be limited to any one or more phases, provided the outline of the additional phase or phases is submitted before such additional phases begin. This does not preclude continuing a subject on the drug from phase 2 to phase 3 without interruption while the plan for phase 3 is being developed.)

Ordinarily, a plan for clinical trial will not be regarded as reasonable unless, among other things, it provides for more than one independent competent investigator to maintain adequate case histories of an adequate number of subjects, designed to record observations and permit evaluations of any and all discernible effects attributable to the drug in each individual treated, and comparable records on any individuals employed as controls. These records shall be individual records for each subject maintained to include adequate information pertaining to each, including age, sex, conditions treated, dosage, frequency of administration of the drug, results of all relevant clinical observations and laboratory examinations made, adequate information concerning any other treatment given and a full statement of any adverse effects and useful results observed, together with an opinion as to whether such effects or results are attributable to the drug under investigation.

11. A statement that the sponsor will notify the Food and Drug Administration if the investigation is discontinued, and the reason therefor.

12. A statement that the sponsor will notify each investigator if a new-drug application is approved, or if the investigation is discontinued.

13. If the drug is to be sold, a full explanation why sale is required and should not be regarded as the com-

mercialization of a new drug for which an application is not approved.

Very truly yours,

(Sponsor)

Per ---

(Indicate authority)

(This notice may be amended or supplemented from time to time on the basis of the experience gained with the new drug. Progress reports may be used to update the notice.)

(3) Each shipment or delivery is made in accordance with the commitments in the "Notice of claimed investigational exemption for a new drug."

(4) The sponsor maintains adequate records showing the investigator to whom shipped, date, quantity, and batch or code mark of each such shipment and delivery, until 2 years after a new-drug application is approved for the drug; or, if an application is not approved, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the Food and Drug Administration has been so notified. Upon the request of a scientifically trained and properly authorized employee of the Department at reasonable times, the sponsor makes the records referred to in this subparagraph and in subparagraph (2) of this paragraph available for inspection, and upon written request submits such records or copies of them to the Food and Drug Administration.

(5) The sponsor monitors the progress of the investigations and currently evaluates the evidence relating to the safety and effectiveness of the drug as it is obtained

from the investigators. Accurate progress reports of the investigations and significant findings, together with any significant changes in the informational material supplied to investigators, shall be submitted to the Food and Drug Administration at reasonable intervals, not exceeding 1 year. All reports of the investigation shall be retained until 2 years after a new-drug application is approved for the drug; or, if an application is not approved, until 2 years after shipment and delivery of the drug for investigational use is discontinued and the Food and Drug Administration so notified. Upon request of a scientifically trained and properly authorized employee of the Department, at reasonable times, these reports shall be made available for inspection, and on written request copies of these reports shall be submitted to the Food and Drug Administration.

(6) The sponsor shall promptly investigate and report to the Food and Drug Administration and to all investigators any findings associated with use of the drug that may suggest significant hazards, contraindications, side-effects, and precautions pertinent to the safety of the drug. If the finding is alarming, it shall be reported immediately and the clinical investigation discontinued until the finding is adequately evaluated and a decision reached that it is safe to proceed.

(7) If the investigations adduce facts showing that there is substantial doubt that they may be continued safely in relation to the drug's potential therapeutic effects, the sponsor shall promptly discontinue the investigation, notify all investigators and the Food and Drug Administration, recall all stocks of the drug outstanding, and furnish the Food and Drug Administration with a full report of the reason for discontinuing the investigation. The Food and Drug Administration will be prepared to confer with the sponsor on the need to discontinue the investigation.

(8) The sponsor shall discontinue shipments or deliveries of the new drug to any investigator who has repeatedly or deliberately failed to maintain or make available his records or reports of his investigations.

(9) The sponsor shall not unduly prolong distribution of the drug for investigational use but shall submit an application for the drug pursuant to section 505(b) of the act (or give reasons for not submitting such application, or a statement that the investigation has been discontinued and the reasons therefor):

(i) With reasonable promptness after finding that the results of such investigation appear to establish the safety and effectiveness of the drug; or

(ii) Within 60 days after receipt of a written request for such an application from the Commissioner.

(10) Neither the sponsor nor any person acting for or on behalf of the sponsor shall disseminate any promotional material representing that the drug being distributed interstate for investigational use is safe or useful for the purposes for which it is under investigation. This regulation is not intended to restrict the full exchange of scientific information concerning the drug including dissemination of scientific findings in scientific or lay communications media; its sole intent is to restrict promotional claims of safety or effectiveness by the sponsor while the drug is under investigation to establish its safety or effectiveness.

(11) The sponsor shall not commercially distribute nor test-market the drug until a new-drug application is approved pursuant to section 505(b) of the the [sic] act.

(12) The sponsor shall obtain from each investigator involved in clinical pharmacology a signed statement in the following form:

Form FD 1572

Department of Health, Education, and Welfare,
Food and Drug Administration
Statement of Investigator
(Clinical Pharmacology)

Name of investigator _____

Date _____

Name of drug _____

To supplier of the drug:

Name _____

Address _____

Dear Sir:

The undersigned, _____, submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and § 130.3 of Title 21 of Code of Federal Regulations as a condition for receiving and conducting clinical pharmacology with a new drug limited by Federal (or United States) law to investigational use.

1. A statement of the education and training that qualifies me for clinical pharmacology.

2. The name and address of the medical school, hospital, or other research facility where the clinical pharmacology will be conducted.

3. The expert committees or panels responsible for approving the experimental project.

4. The estimated duration of the project, and the maximum number of subjects that will be involved.

5. A general outline of the project to be undertaken. (Modification is permitted on the basis of experience

gained without advance submission of amendments to the general outline.)

6. The undersigned understands that the following conditions generally applicable to new drugs for investigational use govern his receipt and use of this investigational drug:

a. The sponsor is required to supply the investigator with full information concerning the preclinical investigation that justifies clinical pharmacology.

b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantity, and use by subjects, and if the clinical pharmacology is suspended or terminated to return to the sponsor any unused supply of the drug.

c. The investigator is required to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the clinical pharmacology.

d. The investigator is required to furnish his reports to the sponsor who is responsible for collecting and evaluating the results, and presenting progress reports to the Food and Drug Administration at appropriate intervals, not exceeding 1 year. Any adverse effects which may reasonably be regarded as caused by, or is probably caused by, the new drug shall be reported to the sponsor promptly; and if the adverse effect is alarming it shall be reported immediately. An adequate report of the clinical pharmacology should be furnished to the sponsor shortly after completion.

e. The investigator shall maintain the records of disposition of the drug and the case reports described above for a period of 2 years following the date of the new-drug application is approved for the drug; or if no application

is to be filed or is approved until 2 years after the investigation is discontinued and the Food and Drug Administration so notified. Upon the request of a scientifically trained and specifically authorized employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying. The names of the subjects need not be divulged unless the records of the particular subjects require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual studies or do not represent actual results obtained.

f. The investigator certifies that the drug will be administered only to subjects under his personal supervision or under the supervision of the following investigators responsible to him, _____, and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

g. The investigator certifies that he will inform any patients or any persons used as controls, of their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

Very truly yours,

_____

(Name of investigator)

_____

(Address)

_____

(13) The sponsor shall obtain from each investigator involved in clinical trials a signed statement in the following form:

Form FD 1573

Department of Health, Education, and Welfare, Food and Drug Administration

Statement of Investigator

Name of investigator_____
Date _____
Name of drug_____

To supplier of drug:
Name _____
Address _____

Dear Sir:

The undersigned, _____, submits this statement as required by section 505(i) of the Federal Food, Drug, and Cosmetic Act and §130.3 of Title 21 of the Code of Federal Regulations as a condition for receiving and conducting clinical investigations with a new drug limited by Federal (or United States) law to investigational use.

1. The following is a statement of my education and experience:

a. Colleges, universities, and medical or other professional schools attended, with dates of attendance, degrees, and dates degrees were awarded.

b. Postgraduate medical or other professional training: Dates, names of institutions, and nature of training.

c. Teaching or research experience: Dates, institutions, brief description of experience.

d. Experience in medical practice or other professional experience: Dates, institutional affiliations, nature of practice, or other professional experience.

e. Representative list of pertinent medical or other scientific publications: Titles of articles, names of publications and volume, page number, and date.

(If this information has previously been submitted to the sponsor, it may be referred to and any additions made to bring it up to date.)

2. If any hospital, institutional, and clinical laboratory facilities, etc., are available and will be employed in conection [sic] with the investigation, an identification of each follows:

(If this information has previously been submitted to the sponsor, reference to the previous submission will be adequate.)

3. The investigational drug will be used by the undersigned or under his supervision in accordance with the plan of investigation described, as follows: (Outline the plan of investigation, including approximation of the number of subjects to be treated with drug and the number to be employed as controls, if any; clinical use to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be undertaken prior to, during, and after administration of the drug; the estimated duration of the investigation; and a description or copies of report forms to be used to maintain an adequate record of the observations and tests results obtained. This plan may include reasonable alternates and variations, and should be supplemented or amended when any significant change in direction or scope of the investigation is undertaken.)

4. The undersigned understands that the following conditions, generally applicable to new drugs for investigational use, govern his receipt and use of this investigational drug:

a. The sponsor is required to supply the investigator with full information concerning the preclinical investigations that justify clinical trials, together with fully informative material describing any prior investigations and experience and any possible hazards, contraindications, side-effects, and precautions to be taken into account in the course of the investigation.

b. The investigator is required to maintain adequate records of the disposition of all receipts of the drug, including dates, quantities, and use by subjects, and if the investigation is terminated to return to the sponsor any unused supply of the drug.

c. The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the drug or employed as a control in the investigation.

d. The investigator is required to furnish his reports to the sponsor of the drug who is responsible for collecting and evaluating the results obtained by various investigators. The sponsor is required to present progress reports to the Food and Drug Administration at appropriate intervals not exceeding 1 year. Any adverse effect that may reasonably be regarded as caused by, or probably caused by, the new drug shall be reported to the sponsor promptly, and if the adverse effect is alarming, it shall be reported immediately. An adequate report of the investigation should be furnished to the sponsor shortly after completion of the investigation.

e. The investigator shall maintain the records of disposition of the drug and the case histories described above for a period of 2 years following the date a new-drug application is approved for the drug; or if the application is not approved, until 2 years after the investigation is discontinued. Upon the request of a scientifically trained and properly authorized employee of the Department, at reasonable times, the investigator will make such records available for inspection and copying. The subjects' names need not be divulged unless the records of particular individuals require a more detailed study of the cases, or unless there is reason to believe that the records do not represent actual cases studied, or do not represent actual results obtained.

f. The investigator certifies that the drug will be administered only to subjects under his personal supervision or under the supervision of the following investigators responsible to him, _____, and that the drug will not be supplied to any other investigator or to any clinic for administration to subjects.

g. The investigator certifies that he will inform any subjects, including subjects used as controls, or their representatives, that drugs are being used for investigational purposes, and will obtain the consent of the subjects, or their representatives, except where this is not feasible or, in the investigator's professional judgment, is contrary to the best interests of the subjects.

Very truly yours,

_____

(Name of investigator)

_____

(Address)

_____

(This form should be supplemented or amended from time to time if new subjects are added or if significant changes are made in the plan of investigation.)

(b) A shipment or other delivery of a new drug that is being imported or is offered for importation into the United States shall be exempt from the requirements of section 505(a) of the act if the following conditions are complied with:

(1) The label of such drug bears the statement "Caution: New drug—Limited by Federal (or United States) law to investigational use"; and

(2) The importer of all such shipments or deliveries is an agent of the foreign exporter residing in the United States or the ultimate consignee, which person has prior to such shipments and deliveries completed and submitted signed copies to the Food and Drug Administration of the "Notice of claimed investigational exemption for a new drug"; and acts as the sponsor of the clinical investigation to assure compliance with the conditions prescribed by paragraph (a) of this section; or

(3) The drug is shipped directly to a scientific institution with adequate facilities and qualified personnel to conduct clinical pharmacology and is intended solely for such use in such institutions and a "Notice of claimed investigational exemption for a new drug" covering this activity has been filed.

(c) Whenever a sponsor submits to the Commissioner the name of an investigator known to the Commissioner as having repeatedly or deliberately failed to comply with the conditions of these exempting regulations, the Commissioner will notify the sponsor that the investigator is not entitled to receive investigational-use drugs, and such investigator shall not be supplied any investigational-use

drug until adequate assurance is provided to and accepted by the Commissioner that the conditions of the exemption will be met. The Food and Drug Administration will be prepared to confer with the sponsor or the investigator, or both, on this point.

(d) If the Commissioner of Food and Drugs finds that:

(1) The submitted "Notice of claimed investigational exemption for a new drug" contains an untrue statement of a material fact or omits material information required by said notice; or

(2) The results of prior investigations made with the drug are inadequate to support a conclusion that it is reasonably safe to initiate or continue the intended clinical investigations with the drug; or

(3) There is substantial evidence to show that the drug is unsafe for the purposes and in the manner for which it is offered for investigational use; or

(4) There is convincing evidence that the drug is ineffective for the purposes for which it is offered for investigational use; or

(5) The methods, facilities, and controls used for the manufacturing, processing, and packing of the investigational drug are inadequate to establish and maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to clinical investigations made with the drug; or

(6) The plan for clinical investigations of the drugs described under section 10 of the "Notice of claimed investigational exemption for a new drug" is not a reasonable plan in whole or in part, solely for a bona fide scientific investigation to determine whether or not the drug is safe and effective for use; or

(7) The clinical investigations are not being conducted in accordance with the plan submitted in the "Notice of claimed investigational exemption for a new drug"; or

(8) The drug is not intended solely for investigational use, since it is being or is to be sold or otherwise distributed for commercial purposes not justified by the requirements of the investigation; or

(9) The labeling or other informational material submitted for the drug as required by section 7 of the "Notice of claimed investigational exemption for a new drug" or any other labeling of the drug disseminated within the United States by or on behalf of the sponsor fails to contain an accurate description of prior investigations or experience and their results pertinent to the safety and possible usefulness of the drug, including all relevant hazards, contraindications, side-effects, and precautions; or any promotional material disseminated within the United States by or on behalf of the sponsor contains any representation or suggestion that the drug is safe or that its usefulness has been established for the purposes for which it is offered for investigations; or

(10) The sponsor fails to submit accurate reports of the progress of the investigations with significant findings at intervals not exceeding 1 year; or

(11) The sponsor fails promptly to investigate and inform the Food and Drug Administration and all investigators of newly found serious or potentially serious hazards, contraindications, side-effects, and precautions pertinent to the safety of the new drug;

he shall notify the sponsor and invite his immediate correction. A conference will be arranged if requested. If

the conditions of exemption are not immediately met, the Commissioner shall notify the sponsor of the termination of the exemption and the sponsor shall recall the unused supplies of the drug.

(e) Where drugs were under clinical trial on man on or after August 10, 1962, the sponsor shall, within 30 days after these regulations become effective, submit a list of such investigational drugs, and within 120 days after such effective date shall submit to the Food and Drug Administration the completed "Notice of claimed investigational exemption for a new drug" or a new-drug application. Failure to do so shall automatically terminate the exemption. If any such clinical trials have been discontinued, the sponsor is requested to submit a statement of why the investigation was discontinued.

(f)(1) A shipment or other delivery of a new drug for laboratory study or animal tests only shall be exempt from section 505(a) of the act if it is labeled: "Caution: New drug—Limited by Federal (or United States) law to laboratory studies and tests on animals. Not for human use." No animals used in such tests, or their products such as milk or eggs, shall be used for food purposes unless the sponsor or the investigator has submitted to the Commissioner data demonstrating that such use will be consistent with the public health, and the Commissioner, proceeding as he would in a matter involving section 409(i) of the act, has notified said sponsor or investigator that the proposed disposition for food purposes is authorized.

(2) The person or firm shipping a new drug for laboratory study or animals tests under this section shall use due diligence to assure that the consignee is regularly engaged in conducting laboratory studies or animal tests

and that the shipment of the new drug will actually be used for laboratory studies or animal testing.

(3) The person who introduced such shipment or who delivered the drug for introduction into interstate commerce maintains adequate records showing the name and post-office address of the expert to whom the drug is shipped, date, quantity, and batch or code mark of each shipment and delivery for a period of 2 years after such shipment and delivery. Upon the request of a properly authorized employee of the Department at reasonable times he makes such records available for inspection and copying.

(g) A "Notice of claimed investigational exemption for a new drug" which pertains to a product subject to the licensing provisions of the Public Health Service Act of July 1, 1944 (58 Stat. 682, as amended; 42 U. S. C. 201 et seq.) should be submitted initially to the Division of Biologics Standards, National Institutes of Health, Public Health Services, rather than to the Commissioner of Food and Drugs. Likewise, amendments of or supplements to such notice, and progress reports, consultations, or other communications with regard to the investigation, should be directed to the Division of Biologics Standards, which monitors the development of biological products subject to license under section 351 of the Public Health Service Act.

(h) Any requirement by this section for the submission of information or data that has been submitted previously may be incorporated by reference.

Effective date. This order shall become effective 30 days from the date of its publication in the Federal Register.

FILE COPY

Office-Supreme Court, U.S.
FILED
DEC 18 1964
JOHN F. DAVIS, CLERK

No. 701

In the Supreme Court of the United States

OCTOBER TERM, 1964

DR. HENRY TUREK AND UROTICA CORPORATION,
PETITIONERS

v.

FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

BRIEF FOR THE UNITED STATES IN OPPOSITION

ARCHIBALD COX,
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In the Supreme Court of the United States

OCTOBER TERM, 1964

No. 701

DR. HENRY TURKEL AND UBIOTICA CORPORATION,
PETITIONERS

v.

FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

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OPINION BELOW

The opinion of the court of appeals (Pet. App. 12) is reported at 334 F. 2d 844.

JURISDICTION

The judgment of the court of appeals was entered on July 21, 1964. A petition for rehearing was denied on September 14, 1964. The petition for a writ of certiorari was filed on November 18, 1964. The jurisdiction of this court is invoked under 28 U.S.C. 1254(1).

757-901—64

QUESTIONS PRESENTED

1. Whether Section 505(h) of the Federal Food, Drug, and Cosmetic Act conferred jurisdiction on the court of appeals to review a decision of the Commissioner of Food and Drugs refusing to grant an investigational exemption from the new drug application requirements.

2. Whether the judgment of the court of appeals dismissing petitioners' appeal for lack of jurisdiction violated petitioners' right to due process under the Fifth Amendment to the Constitution.

STATUTE INVOLVED

Section 505 of the Federal Food, Drug, and Cosmetic Act, 52 Stat. 1052, as amended, 21 U.S.C. 355 (Supp. V), provides in pertinent part:

> (a) No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) is effective with respect to such drug.
>
> (b) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such persons shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use; (2) a full list of the articles used as components of such drug; (3) a full statement of the composition of such drug; (4) a full description of the methods used in, and the facilities and controls used for, the manufacture, processing, and packing

of such drug; (5) such samples of such drug and of the articles used as components thereof as the Secretary may require; and (6) specimens of the labeling proposed to be used for such drug.

(c) Within one hundred and eighty days after the filing of an application under this subsection, or such additional period as may be agreed upon by the Secretary and the applicant, the Secretary shall either—

(1) approve the application if he then finds that none of the grounds for denying approval specified in subsection (d) applies, or

(2) give the applicant notice of an opportunity for a hearing before the Secretary under subsection (d) on the question whether such application is approvable. If the applicant elects to accept the opportunity for hearing by written request within thirty days after such notice, such hearing shall commence not more than ninety days after the expiration of such thirty days unless the Secretary and the applicant otherwise agree. Any such hearing shall thereafter be conducted on an expedited basis and the Secretary's order thereon shall be issued within ninety days after the date fixed by the Secretary for filing final briefs.

* * * * *

(h) An appeal may be taken by the applicant from an order of the Secretary refusing or withdrawing approval of an application under this section. Such appeal shall be taken by filing in the United States court of appeals for

the circuit wherein such applicant resides or has his principal place of business, or in the United States Court of Appeals for the District of Columbia Circuit, within sixty days after the entry of such order, a written petition praying that the order of the Secretary be set aside. * * *

(i) The Secretary shall promulgate regulations for exempting from the operation of the foregoing subsections of this section drugs intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs. Such regulations may, within the discretion of the Secretary, among other conditions relating to the protection of the public health, provide for conditioning such exemption upon—

(1) the submission to the Secretary, before any clinical testing of a new drug is undertaken, of reports, by the manufacturer or the sponsor of the investigation of such drug, of preclinical tests (including tests on animals) of such drug adequate to justify the proposed clinical testing;

(2) the manufacturer or the sponsor of the investigation of a new drug proposed to be distributed to investigators for clinical testing obtaining a signed agreement from each of such investigators that patients to whom the drug is administered will be under his personal supervision, or under the supervision of investigators responsible to him, and that he will not supply such drug to any other investigator,

or to clinics, for administration to human beings; and

(3) the establishment and maintenance of such records, and the making of such reports to the Secretary, by the manufacturer or the sponsor of the investigation of such drug, of data (including but not limited to analytical reports by investigators) obtained as the result of such investigational use of such drug, as the Secretary finds will enable him to evaluate the safety and effectiveness of such drug in the event of the filing of an application pursuant to subsection (b).

* * * * *

STATEMENT

Petitioners are the developers and distributors of thirteen separate drugs collectively known as the "'U' Series Drugs," which are intended for use in the treatment of mongolism (R. 11a–12a).* The drugs are "new drugs" within the meaning of Section 201(p) of the Federal Food, Drug, and Cosmetic Act, 52 Stat. 1041, as amended, 21 U.S.C. 321(p) (Supp. V). Under the provisions of Section 505(a) of the Act, no "new drug" may be introduced into interstate commerce unless an approved "new drug" application is in effect with respect to it. Other provisions of Section 505 prescribe procedures for obtaining approval of an application. No such application has been approved or is pending with respect to petitioners' drugs.

*Record references are to petitioners' printed Motion for Stay, filed with the court of appeals and made a part of the record in this Court.

Section 505(i) grants a limited exemption from the application requirements, conditioned on compliance with regulations promulgated by the Secretary, for drugs "intended solely for investigational use by experts qualified by scientific training and experience to investigate the safety and effectiveness of drugs."

Petitioners submitted to the Commissioner of Food and Drugs a notice claiming an exemption under Section 505(i) for the "U" Series Drugs (R. 5a). On submission of the notice the exemption became conditionally effective. The Commissioner notified petitioners that their notice was deficient (R. 2a), and petitioners corrected some but not all of the deficiencies. Thereafter, the Commissioner notified petitioners that "the conditions of exemption have not been met, and the exemption allowing clinical testing of the drug is terminated." Petitioners were advised that distribution and administration of the drugs to humans should immediately be discontinued (R. 1a). The Commissioner's action was discussed at an informal meeting between petitioners and representatives of the Food and Drug Administration but no change of position resulted.

The petitioners filed a petition to review the Commissioner's action in the court of appeals, invoking the court's jurisdiction on the basis of Section 505(h) of the Act. Respondent filed a motion to dismiss the petition on the ground that the court of appeals lacked jurisdiction to review the termination of an investigational drug exemption. After oral argument, judgment was entered dismissing the petition. The court of appeals held that the right of appeal granted

by Section 505(h) applies only to an order refusing or withdrawing approval of a new drug application and that the denial of an exemption under Section 505(i) could not be reviewed except by appeal from a subsequent denial of a new drug application. 334 F. 2d at 845–846.

ARGUMENT

1. It is clear from an examination of Section 505 that the provision of subsection (h) for review of "an order * * * *refusing or withdrawing approval of an application* under this section" (emphasis added) was intended to cover only new drug applications filed under subsection (b) and not action taken with respect to a request for an investigational exemption under subsection (i). The only "application" mentioned in the section is a new drug application, which is also the only document for which "approval" is expressly required (Sec. 505(a)) and for which there is provision for orders "refusing" (Sec. 505(d)) or "withdrawing" (Sec. 505(e)) approval.

Subsection (i) of Section 505, which provides for the investigational exemption, is placed *after* the provisions for review. Clearly, if Congress had intended to provide for review of actions taken under subsection (i) on the same footing as orders refusing or withdrawing approval of a new drug application, it would not have placed the provision for review where it did. Moreover, subsection (i) begins with a direction to the Secretary to promulgate regulations exempting drugs intended solely for investigational use "from the operation *of the foregoing subsections*"

(emphasis added), a reference which includes the provisions for review in subsection (h).

2. Petitioners' contention that the denial without a hearing of an investigatory exemption and the withholding of judicial review of such denial deprived them of due process of law is without merit. As this Court has repeatedly stated, "The demands of due process do not require a hearing, at the initial stage or at any particular point or at more than one point in an administrative proceeding so long as the requisite hearing is held before the final order becomes effective." *Opp Cotton Mills, Inc.* v. *Administrator,* 312 U.S. 126, 152–153. *Accord, Lichter* v. *United States,* 334 U.S. 742, 791–792; *Ewing* v. *Mytinger & Casselberry, Inc.,* 339 U.S. 594, 598. Petitioners have a full opportunity under the statute for a hearing (Sec. 505(c)) and for judicial review of the final administrative decision. The statutory scheme requires no more of petitioners, who have been denied an exemption from the requirement that new drug applications be filed and approved, than that they proceed with an application for approval of their drugs and thus develop a record which can be judicially reviewed.

CONCLUSION

For the foregoing reasons, it is respectfully submitted that the petition for a writ of certiorari should be denied.

ARCHIBALD COX,
Solicitor General.

HERBERT J. MILLER, JR.,
Assistant Attorney General.

BEATRICE ROSENBERG,
JERRY H. OPACK,
Attorneys.

DECEMBER 1964.

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PETITIONERS' REPLY BRIEF.

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ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT.

PETITIONERS' REPLY BRIEF.

Petitioners, under and by virtue of the provisions of Rule 24 of this Court, herewith present this Reply Brief directed to the Brief of the United States in Opposition heretofore filed.

OPINION BELOW.

The opinion of the Court of Appeals (Pet. App. 12) is reported at 334 F. 2d 844.

JURISDICTION.

The judgment of the Court of Appeals was entered on July 21, 1964. A petition for rehearing was denied on September 14, 1964. The Petition for a Writ of Certiorari was filed on November 18, 1964. The Brief for the United States in Opposition was filed on December 18, 1964. The jurisdiction of this Court is invoked under 28 U. S. C. 1254(1).

QUESTIONS PRESENTED.

In a suit filed under the provisions of 21 U. S. C. 355-(h), providing for a Petition to Review an order withdrawing approval of an application granting an exemption for the investigational use of a drug, the Court of Appeals for the Sixth Circuit granted the Respondent's Motion to Dismiss said Petition to Review. The Court of Appeals stated in its decision that there was no recourse available to the Petitioners to review the order of the Food and Drug Administration, issued against the Petitioners. The Court of Appeals further made a finding that a tendered record of the Food and Drug Administration could not be received by the Court for its consideration in connection with the issues presented in this cause. The questions presented are:

1. Whether the 1962 Amendments to the Food and Drug Act that the right of appeal to the United States Court of Appeals granted by 21 U. S. C., Section 355(h), applied to an order of the Secretary, Health, Education and Welfare Department, withdrawing approval of an investigational exemption granted permitting the distribution of a drug for investigational use.

2. Whether Section 262 of the Judicial Code grants jurisdiction to federal courts to review an order of the Secretary, Health, Education and Welfare Department, withdrawing approval of an investigational exemption granted permitting the distribution of a drug for investigational use.

3. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution protects against unreasonable and unwarranted conditions imposed

by regulations adopted by a federal agency under a directive contained in an Act of Congress.

4. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution protects against an unreasonable and unwarranted interference in the investigational use of a drug, when all of the medical evidence available with respect to the investigational use of said drug indicates that the same is devoid of harmful effects, and beneficial to those patients being administered the same.

5. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution protects against a proceeding, where an investigational use exemption is withdrawn by the Food and Drug Administration, without a hearing, without confrontation, and without an opportunity to present evidence germane to the subject matter, before such time as a final order of the Food and Drug Administration is issued with respect to the termination of the investigational use exemption in existence.

6. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution protects duly licensed physicians against the unbridled and arbitrary use of power by the Food and Drug Administration in refusing to present and disclose reasons upon which is premised an order of termination of an existing exemption authorizing the investigational use of a drug.

7. Whether the Due Process Clause of the Fifth Amendment of the U. S. Constitution requires a judicial review of proceedings conducted by a federal agency, wherein said federal agency denies a hearing,

confrontation and findings before a final order is issued to Petitioners.

In the Brief for the United States in Opposition, under the subtitle "Questions Presented," paragraph 2 (Resp. Brief 2), the following appears:

> "2. Whether the judgment of the court of appeals dismissing petitioners' appeal for lack of jurisdiction violated petitioners' right to due process under the Fifth Amendment to the Constitution."

This question is not directly involved in this case, nor is this question invoked, by the Petitioners. Rather the question propounded, in relation to the guarantees of the Fifth Amendment to the Constitution are whether the said Amendment protects against

> (a) "* * * unreasonable and unwarranted conditions imposed by regulations adopted by a federal agency, under a directive contained in an Act of Congress," or
>
> (b) "* * * an unreasonable and unwarranted interference in the investigational use of a drug, when all of the medical evidence available with respect to the investigational use of said drug indicates that the same is devoid of harmful effects, and beneficial to those patients being administered the same," or
>
> (c) "* * * a proceeding, where an investigational use exemption is withdrawn by the Food and Drug Administration, without a hearing, without confrontation, and without an opportunity to present evidence germane to the subject matter, before such time as a final order of the Food and Drug Administration is issued with respect to the termination of the investigational use exemption in existence."

And whether the said Amendment

> (d) "* * * protects duly licensed physicians against the unbridled and arbitrary use of power by

the Food and Drug Administration in refusing to present and disclose reasons upon which is premised an order of termination of an existing exemption authorizing the investigational use of a drug," and

(e) "* * * requires a judicial review of proceedings conducted by a federal agency, wherein said federal agency denies a hearing, confrontation and findings before a final order is issued * * *."

CONSTITUTION, STATUTES, FEDERAL RULES AND REGULATIONS INVOLVED.

Involved herein are the following: Amendment V, U. S. Constitution, set forth in the Appendix (Pet. App. 18); Federal Food, Drug and Cosmetic Act, as amended, 21 U. S. C. 355, set forth in the Appendix (Pet. App. 19-27); Regulations adopted by the Food and Drug Administration, 28 Federal Register, 170-182, 319, 5048 (21 C. F. R. 130.3), set forth in the Appendix (Pet. App. 27-48); and Rules 26 and 33 of the Federal Rules of Civil Procedure.

SUPPLEMENTAL STATEMENT.

The Petitioners, the Court of Appeals, and this Court, are seriously handicapped at this point, because of the fact that the Respondent, Food and Drug Administration, has not placed in the Record, and has not been required to file in the Record, all material, writings, documents, communications and other indicia of evidence, with respect to its evaluation of the "U" Series Drugs.

However, the Petitioners have in their possession, copies of some of the writings of the Respondent, with respect to its actions and attitudes toward the "U" Series Drugs; and there is attached hereto the following:

Exhibit 1A. This is a reproduction of a letter issued by the Respondent by its Medical Officer, Divi-

sion of New Drugs, Bureau of Medicine, one Jean D. Lockhart, M. D., addressed to the Petitioners, dated August 2, 1963, which states in part as follows:

> *"In summary, there is no basis for considering that the random, empirical and scientifically irrational choice of drugs and dosages contained in this NDA is either safe or effective in the management of Mongolism. It is our opinion that it may be impossible to write suitable labeling for efficacy for this product;* **in view of the cytogenetic basis of Mongolism, we recommend that you abandon work on this application."** (Emphasis added.)

Exhibit 2A. This is a reproduction of a letter transmitted by Richard L. Masland, M. D., Director, National Institute of Neurological Diseases and Blindness, National Institutes of Health, to Hon. John E. Fogarty, M. C., dated March 3, 1964, which states in part as follows:

> *"The drugs included in Dr. Turkel's "U Series" are well-known compounds. On theoretical grounds, and based on the known effects of these drugs, which consist of vitamins, minerals, and other medications, our advisors have stated that, although they are not harmful, they doubt the drugs would be of specific value in treating mongolism. However, because of Dr. Turkel's claims, both Dr. Bailey, former Institute director, and I have met with him to discuss his treatment and the type of results he has observed in treated patients. The Institute has also tried, without success to find investigators willing to devote the time required to the scientific evaluation of the Turkel therapy."*

Petitioners have labored since 1943 in the development of the "U" Series Drugs, which are directed toward treatment of the condition resulting from inborn error metabolism. (Exhibits 3A and 4A.)

Hence we reiterate that the opinion and judgment of the Court of Appeals in effect held that there is no protection to the Petitioners in this case, where all of the procedural requirements of due process were ignored and denied by the arbitrary, unwarranted and summary action of the Food and Drug Administration.

REASONS FOR GRANTING THE WRIT.

Petitioners respectfully incorporate by reference the statements made under this heading heretofore (Pet. App. 7-10).

CONCLUSION.

For the reasons set forth above, supplementing those contained in the Petitioners' Application, it is respectfully submitted that the Petition for a Writ of Certiorari should be granted.

LEO E. RATTAY,
Counsel for Petitioners.

EXHIBIT 1A.

DEPARTMENT OF

HEALTH, EDUCATION, AND WELFARE

FOOD AND DRUG ADMINISTRATION

Washington 25, D. C.

NDA 14-712

Aug. 2, 1963

Ubiotica Corporation
Attention: Dr. Henry Turkel
8000 West Seven Mile Road
Detroit 21, Michigan

Gentlemen:

Reference is made to your new drug application dated May 29, 1963 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation "'U' Series Drugs."

The application is incomplete under section 505(b)(1) and (6) as follows:

No scientific evidence is supplied that these drugs have altered the mongoloid condition of the children who are treated. No diagnostic studies are documented. Laboratory work is conspicuous by its absence. For example, there is no way of determining the original thyroid status of children who are being treated with thyroglobulin and tri-iodothyronine. Metrazol is used as one component of the Series although electroencephalograms are never mentioned in the NDA. At least four of the 15 "Investigators" for the drug are not medical doctors, and it is evident that the others are not bone fide investigators in any scientific sense but merely agents who administer the drug. No rationale is given for the choice of the 51 component ingredients of this "Series" or their dosages. No evidence is offered that mongoloid patients have nutritional or hormonal requirements different from normal subjects. No recognition is made of the cytogenetic basis of mongolism.

In summary, there is no basis for considering that the random, empirical and scientifically irrational choice of drugs and dosages contained in this NDA is either safe or effective in the management of Mongolism. It is our opinion that it may be impossible to write suitable labeling for efficacy for this product; *in view of the cytogenetic basis of Mongolism, we recommend that you abandon work on this application.*

The application is not approvable in accordance with section 130.5(a) of the New Drug Regulations, and may not be filed since it is incomplete on its face in that it does not contain all the matter required by sections 505(b)(1), (2), (3), (4), (5) and (6) of the Act.

Since the application is incomplete under section 505 (b)(1), (2), (3), (4), (5) and (6) of the Act, it may not be filed as an application provided for in section 505(b).

Sincerely yours,

JEAN D. LOCKHART, M.D.
Medical Officer
Division of New Drugs
Bureau of Medicine

EXHIBIT 2A.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
Bethesda 14, Md.

Mar. 3, 1964.

Dear Mr. Fogarty:

This is in reply to your request for comment on the letter of Mr. and Mrs. Ervin Ronell of Elk Point, South Dakota, concerning the use of the "U Series" of drugs for the treatment of mongolism (Down's syndrome).

From time to time, as I am sure you know, various special diets and supplementary materials have been reported beneficial for mongoloid children. Research studies to date, however, have not demonstrated that such treatment is of specific value for this disorder.

Experience has shown repeatedly that the performance of the mongoloid child is significantly influenced by active encouragement, attention, and good general care. Many of the reputed effects of specific treatment have subsequently been shown to result from the nonspecific stimulation which the treated child received from those interested in observing the results of therapy.

The drugs included in Dr. Turkel's "U Series" are well-known compounds. On theoretical grounds, and based on the known effects of these drugs, which consist of vitamins, minerals, and other medications, our advisors have stated that, *although they are not harmful,* they doubt the drugs would be of specific value in treating mongolism. However, because of Dr. Turkel's claims, both Dr. Bailey, former Institute director, and I have met with him to discuss his treatment and the type of results he has observed in treated patients. *The Institute has also tried, without success to find investigators willing to devote the time required to the scientific evaluation of the Turkel therapy.*

A recently completed independent study in Buffalo on the "U Series" drugs revealed no improvement in 12 children treated with the Series for a 1-year period. I am enclosing a copy of the report on this investigation as published in the Journal of the American Medical Association, February 1, 1964.

Of course, as you are aware, licensing and distribution of the Turkel drugs is under the authority of the Food and Drug Administration, in compliance with the drug-testing provisions of the law. As I understand, the U-Series medication may be distributed to qualified medical investigators for bona fide clinical study at any time. FDA, I am sure, can provide you with other information in this matter.

I hope these comments will prove useful to you. Please let us know if we can be of further help.

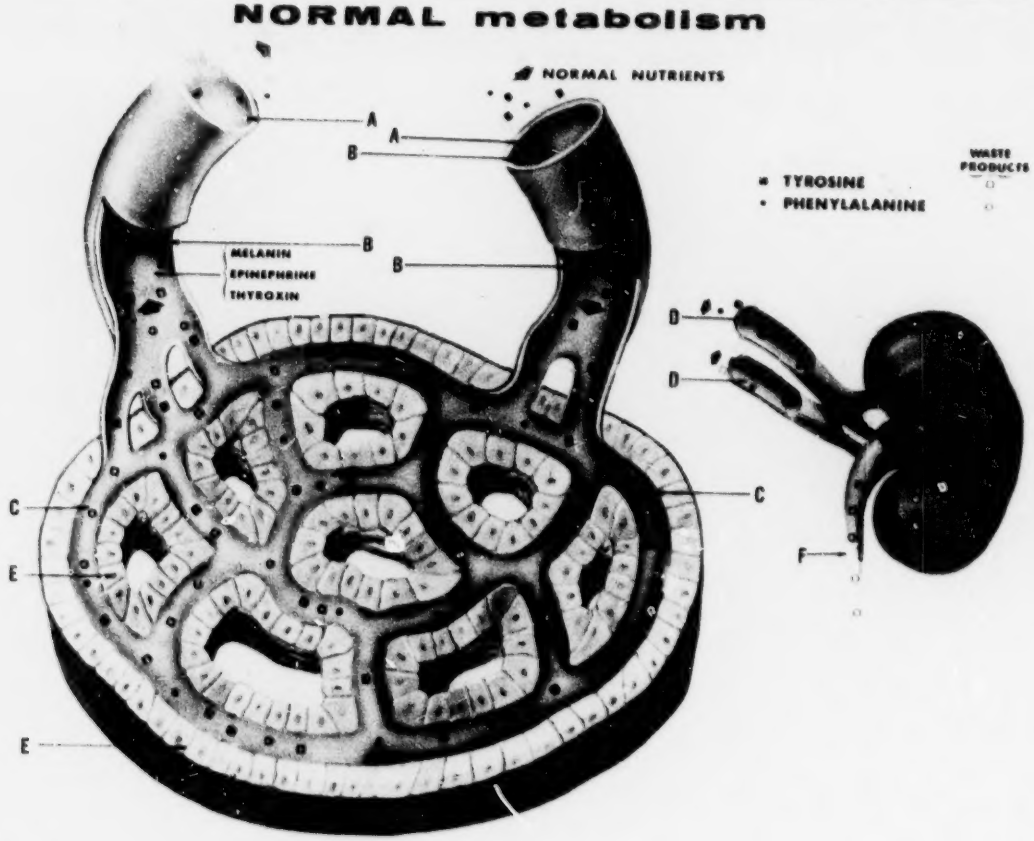
Sincerely yours,

RICHARD L. MASLAND, M.D.
Director, National Institute of Neurological Diseases and Blindness

Honorable John E. Fogarty
House of Representatives
Washington, D. C. 20515

Enclosure

EXHIBIT 3A.



NORMAL METABOLISM

A—Potential space for circulating blood, nutrients, hormones, waste products, etc.

B—Arteries and veins NOT blocked by harmful metabolites.

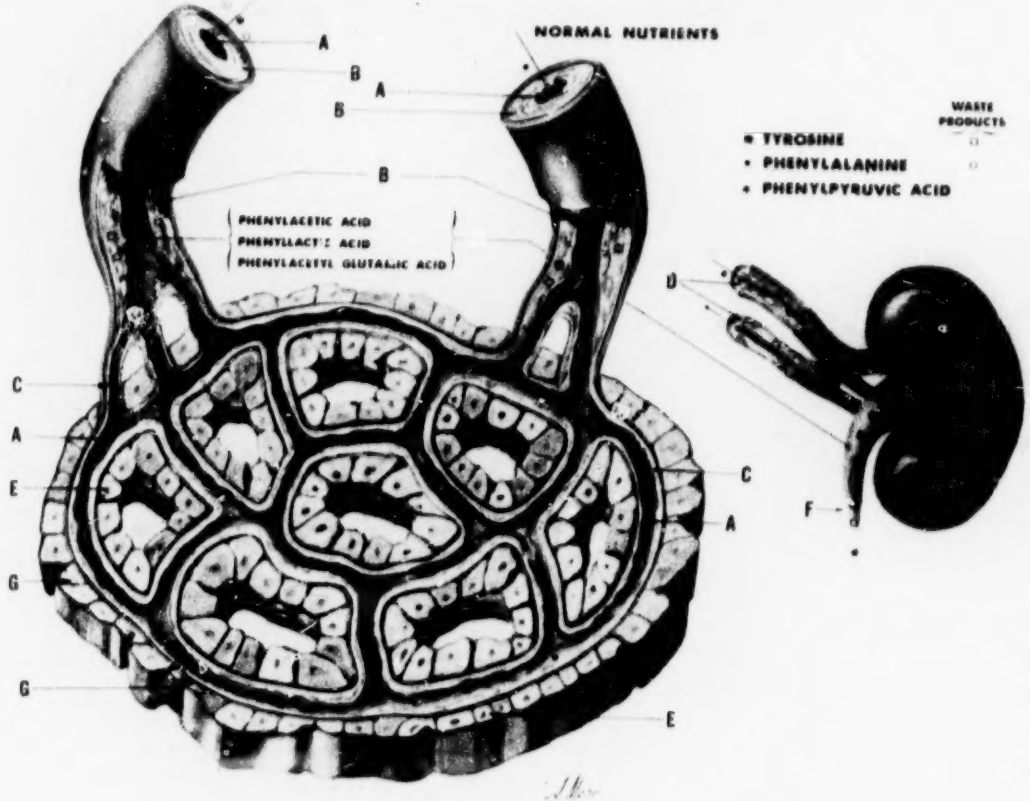
C—Arteries and veins within organs and tissues NOT blocked by harmful metabolites.

D—Renal arteries and veins NOT blocked by harmful metabolites.

E—Organs and tissues grow, mature and function at normal rate in a "timely" manner.

F—Urine contains normal waste products.

INBORN ERROR metabolism



BY HENRY TURKEL 1964

INBORN ERROR METABOLISM

A—Less space available for circulating blood, nutrients, hormones, waste products, etc.

B—Arteries and veins BLOCKED by harmful metabolites.

C—Arteries and veins within organs and tissues BLOCKED by harmful metabolites.

D—Renal arteries and veins are BLOCKED by harmful metabolites.

E—Organs and tissues grow, mature and function at lower rate as result of receiving an insufficient amount of nutrients, etc.

F—Urine contains fewer normal products plus unmetabolized normal and alternate metabolites and their abnormal products.

G—Organs and tissues deprived of nutrients, hormones, etc., as well as affected by harmful metabolites grow, mature and function at a lower rate and untimely manner with resultant inborn structural anomalies characteristic of inborn errors of metabolism, e.g. mongolism, arteriosclerosis, phenylketonuria, etc.

EXHIBIT 4A.

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PETITION FOR REHEARING.

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Exhibit 1. Legislative History of 1962 Amendments of the Federal Food, Drug and Cosmetic Act, 21 U. S. C. 355:

(a) Excerpts from proceedings of the U. S. Senate, October 3, 1962, Pages 22038, 22039 and 22040, Congressional Record 6

(b) Excerpts from proceedings of the U. S. House of Representatives, October 4, 1962, Pages 22320-22321, Congressional Record 12

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FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE,

Respondent.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT.

PETITION FOR REHEARING.

Petitioner presents its petition for a rehearing of this Court's order dated January 25, 1965, denying the Petition for a Writ of Certiorari to the United States Court of Appeals for the Sixth Circuit, and, in support thereof, respectfully shows:

GROUNDS FOR REHEARING.

1. That Petitioners in this cause have attempted to invoke the jurisdiction of the federal courts, only after a complete exhaustion of the administrative remedies available to them, and only after the subsequent entry by the Food and Drug Administration of a final administrative order.

2. Under the facts in this cause, the refusal of the federal courts to take jurisdiction, in effect, states the

proposition of law, that the Food and Drug Administration, in the enforcement and implementation of the 1962 Amendments to the Federal Food, Drug and Cosmetic Act, is empowered to determine whether the investigational use of any drug or medicine may be conducted, in its sole discretion, and without any right whatever to a review of its determination in the matter.

3. The effect of the decision of the Circuit Court of Appeals thus may constitute an addendum to the 1962 Amendments to the Federal Food, Drug and Cosmetic Act, to-wit: That the Food and Drug Administration has the sole and complete right and power to determine the scientific progress to be made in the future, in that the Food and Drug Administration may arbitrarily, and without any review of its judgment, determine what new drugs may be involved in investigational use, which is a prerequisite for a New Drug Application under the Statutes.

4. In the event that the decision of the Circuit Court of Appeals stands, the Food and Drug Administration can continue to subvert, and act completely contrary to the intention, purpose and direction as determined by Congress in the enactment of the 1962 Amendments to the Federal Food, Drug and Cosmetic Act.

SUPPLEMENTAL STATEMENT.

The Petitioners respectfully reiterate that all available administrative remedies have been exhausted with respect to the continued investigational use of the "U" Series Drugs.

It is respectfully reiterated that the Respondent, Food and Drug Administration, has taken an arbitrary and unreasonable position with respect to the physical abnormality to which the "U" Series Drugs are directed; and such position is recited on page 6, Petitioners' Reply Brief herein; and in part is as follows:

> "* * * It is our opinion that it may be impossible to write suitable labels for efficacy for this product; *in view of the cytogenetic basis of Mongolism, we recommend that you abandon work on this application.*" (Emphasis added.)

This position of the Food and Drug Administration has been rendered absolute and irreversible as a result of the Court's refusal to take jurisdiction over this matter. Thus the medical opinion and judgment of a few doctors of medicine employed by the Food and Drug Administration is absolute and final and upheld; in contradistinction to the medical judgment and investigational results of more than fifty doctors of medicine, who, by and large, are experts in this particular field of medicine.

The facts are that the Food and Drug Administration is thus given the right to state to the estimated five million persons now living in the United States and an estimated 126,000 persons born each year, that they have a condition which because of its "cytogenetic basis," should not be considered in the annals of scientific investigation with the goal in mind to alleviate or treat said physical condition.

There is appended hereto excerpts from the proceedings of Congress, which set forth the intent of Congress as

to the enactment and implementation of the 1962 Amendments to the Federal Food, Drug and Cosmetic Act, 21 U. S. C. 355; and as set forth therein the objective of the 1962 Amendments is:

> "* * * to prevent production under insanitary conditions and to require that the methods used in drug manufacture conform to and are operated and administered in conformity with 'current good manufacturing practice' to the end that the drug 'has the safety and has the identity and strength and meets the quality and purity characteristics which it purports or is reported to possess.'" (Congressional Record—Senate—88th Congress—page 22038.)

Accordingly, it is respectfully reiterated that the opinion and judgment of the Court of Appeals should be reversed and jurisdiction assumed by the Court to review this significant and important cause.

CONCLUSION.

For the foregoing reasons it is respectfully urged that this petition for a rehearing be granted, and that, upon further consideration, writ of certiorari issue to the United States Court of Appeals for the Sixth Circuit.

LEO E. RATTAY,
Counsel for Petitioners.

CERTIFICATE OF COUNSEL.

I, Leo E. Rattay, counsel for the above-named petitioners, do hereby certify that the foregoing petition for rehearing is presented in good faith and not for delay, and that it is restricted to the grounds specified in Rule 58, Subdivision 2, of the Rules of this Court.

LEO E. RATTAY,
Counsel for Petitioners.

EXHIBIT 1.

LEGISLATIVE HISTORY OF 1962 AMENDMENTS OF THE FEDERAL FOOD, DRUG AND COSMETIC ACT, 21 U. S. C. 355.

(a) Excerpts from proceedings of the U. S. Senate, October 3, 1962, Pages 22038, 22039 and 22040, Congressional Record.

SECTION 101—REQUIREMENT OF ADEQUATE CONTROLS IN MANUFACTURING

On this subject the language of the Senate and House bills was identical. The objective is to prevent production under insanitary conditions and to require that the methods used in drug manufacture conform to and are operated and administered in conformity with "current good manufacturing practice" to the end that the drug "has the safety and has the identity and strength and meets the quality and purity characteristics which it purports or is reported to possess."

As the Judiciary Committee had stated:

> The committee decided to provide that not only must the requisite methods, facilities and quality controls be established in conformity with current good manufacturing p actice, but that these methods, facilities and controls must in fact be operated and administered in conformity with current good manufacturing practice.

SECTION 102—EFFECTIVENESS AND SAFETY OF NEW DRUGS

In this important area the language of the Senate and House bills was again identical, with one minor exception. One of the grounds in this section for withholding or withdrawing approval of a new drug application was if, in the

language of the Senate bill, "such labeling is false or misleading in any particular." In the House bill the correlative language was "based on a fair evaluation of all material facts such labeling is false or misleading in any particular." The Senate conferees acceded to the House and the phrase "based on a fair evaluation of all material facts" is contained in the bill reported by the conferees. The grounds of inserting this phrase were stated to be the desire to obviate the possibility that a new drug application would be disapproved or withdrawn arbitrarily or capriciously because of some minor or trivial statement that could be easily corrected but at the same time construed to be false or misleading. This is not a substantive change but an effort to make explicit what would undoubtedly be the case in any event.

Section 103—Records and Reports as to Experience on New Drugs—Approved New Drugs

Both the House and Senate bills added a new provision to the new drug section of the Food and Drug Act requiring drug manufacturers to keep records and make reports as to experience with drugs now on the market. The Senate bill required that in promulgating regulations establishing any recordkeeping and reporting system under this section, the Secretary "shall have due regard for the professional ethics of the medical profession and the interests of patients." In addition the Senate bill authorized the Secretary, where he deemed it appropriate, to furnish drug manufacturers with information on their product that came to the Secretary from sources other than the manufacturer. The House bill contained neither of these provisions. They were accepted by the conferees.

Experimental Use of Drugs

Both the House and Senate bills contain provisions empowering FDA to require drug manufacturers to keep records and make reports on clinical experience with regard to experimental drugs prior to the submission of a new drug application for such product. The keeping of these records and making of reports is made a condition precedent to any experimental program conducted by a drug manufacturer (Italics added). The Senate bill authorized the Secretary to require adequate tests on animals before the drug could be tested on human beings. The House bill contained a similar provision authorizing adequate preclinical tests prior to use of humans. While the House provision was accepted by the conferees, it was specifically provided that "preclinical tests" would include "adequate tests in animals."

The Senate bill also authorized the Secretary to require drug investigators to register with the Secretary. The House bill contained no similar provision and it was not adopted by the conferees. The Senate bill authorized the Secretary to require drug investigators to furnish him with simultaneous copies of their reports to the manufacturer on their experiments with an experimental drug. The House bill, on the other hand, specifically rules out any requirement of direct submission of reports to the Secretary by investigators. The conferees accepted a compromise between the two versions whereby analytical reports made by investigators to the drug manufacturers will be considered as part of the data the Secretary can require drug manufacturers to furnish him prior to the submission of the new drug application in order to enable him to evaluate the safety and effectiveness of the drug in the event a new drug application for it is filed. This new requirement on experimental-use drugs puts a firm legis-

lative and statutory base under FDA existing regulatory power.

With regard to patient consent the Senate bill required that investigators shall have due regard to the "interest of patients," while the House bill specifically required that regulations on experimental-use drugs must condition the use of such drugs on the patient's consent to such use. The conferees adopted substituted language which requires the Secretary of HEW to include in his regulations an experimental drug provision for obtaining patient consent, "except where obtaining such consent would not be feasible, or in the professional judgment of the investigator would be contrary to the best interest of the patient."

The Senator from Nebraska offered the compromise language, and after some rearrangement, it was adopted. It was satisfactory and solved one of the very difficult problems we had in the conference.

The conclusion reached by the conferees with regard to records and reports on new drugs, including experimental drugs, are also applicable to Section 106, Records and Reports as Experience on Antibiotics.

Section 104—New Drug Clearance Procedure

There was only one difference between the Senate and House language with respect to the new drug clearance procedure. Both bills provided that a new drug application cannot become effective automatically under any circumstances but must be affirmatively approved. Both provided that the Secretary initially has 180 days—unless further extended by agreement—in which to decide to approve the application or to give notice of an opportunity for a hearing; that the applicant has 30 days in which to request a hearing; and that the hearing would have to

begin within 90 days after such 30 days, or within a total of 120 days after notice of the opportunity of a hearing. The Senate bill did not set forth any time period by which an order would have to be entered following the hearing. The House bill required the order to be issued in 90 days after the completion of the hearing. A compromise was worked out to the effect that the order would have to be issued within 90 days, not after the hearing, but after the date fixed by the Secretary for filing final briefs. This is the last step in the hearing process prior to the final decision of the Secretary.

I personally felt that the Senate bill, which put no limit on the time that the HEW could take after the hearing, was preferable, but I trust that the present provision will be adequate.

The conferees also accepted a House provision which would correct a needless and unintentional inequity in the application of the food additive anticancer proviso to additives for animal feed, while preserving in its full vigor the consumer protection now afforded by that provision.

The provision stipulates that the anticancer proviso of existing law shall not apply with respect to the use of a substance—for example, a veterinary drug—as an ingredient of feed for animals which are raised for food production, if the Secretary finds, first, that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended; and, second, that no residue of the additive will be found in any edible portion of such animals after slaughter or in any food product of the living animal—such as milk or eggs.

Another amendment would similarly amend the basic act—which is the corresponding anticancer clause con-

tained in the color additive amendment of 1960 to the basic act.

It should be emphasized that where a new drug is involved in these fields and subsequent information and new evidence raise a question as to its safety, it can be withdrawn under the new withdrawal and suspension powers provided for in Section 102 of the bill.

Section 202—Confidentiality of Information Obtained by Inspection

The House bill extended the scope of the confidentiality requirements in Section 301(j) of the Food, Drug, and Cosmetic Act, but made a special provision to the effect that "nothing in this act shall authorize the withholding of information from the duly authorized committees of the Congress." The conferees decided to strike the confidentiality provsion entirely from the bill and to leave the law on this matter as it is.

The Senate Subcommittee on Antitrust and Monopoly has in the past had no difficulty in securing information from the Food and Drug Administration and has never wished to secure information of the type prohibited by the present law; namely, information relating to "any method or process which as a trade secret is entitled to protection." It is expected, of course, that since the Congress is not making the law more restrictive on this matter, the FDA will not make its interpretation and administration of Section 301(j) more restrictive. Congress and the public deserve to have access to information in the Food and Drug Administration which is not of the nature of a trade secret and is in the public interest.

(b) Excerpts from proceedings of the U. S. House of Representatives, October 4, 1962, Pages 22320-22321, Congressional Record.

STATEMENT

The managers on the part of the House at the conference on the disagreeing votes of the two Houses on the amendments of the House to the bill (S. 1552) to amend and supplement the laws with respect to the manufacture and distribution of drugs, and for other purposes, submit the following statement in explanation of the effect of the action agreed upon by the conferees and recommended in the accompanying conference report:

The House struck out all of the Senate bill after the enacting clause and inserted a substitute amendment.

The committee of conference has agreed in a substitute for both the Senate bill and the House amendment. Except for clarifying, clerical, and conforming changes, the differences are noted below:

EFFECTIVENESS AND SAFETY OF NEW DRUGS

Both the House amendment and the Senate bill required the Secretary of Health, Education, and Welfare to refuse to approve, or to withdraw approval, of a new drug if he found that there was a lack of substantial evidence (as defined) of the effectiveness of the drug for its proposed use, or if he found that the labeling was false or misleading in any particular. The House version required that the finding as to false or misleading labeling be "based on a fair evaluation of all material facts"; the Senate version did not contain the quoted phrase. The conference substitute accepts the House version on this point.

RECORDS AND REPORTS AS TO EXPERIENCE ON NEW DRUGS

Existing law provides that the Secretary of Health, Education, and Welfare shall promulgate regulations for exemption of new drugs from the new drug clearance requirement otherwise applicable under Section 505(1) of the Federal Food Drug, and Cosmetic Act, where such drugs are to be used solely for investigational purposes by qualified experts. The House version provided that regulations of the Secretary could condition such exemption for investigational use of drugs (1) upon submission to him, by the manufacturer or sponsor of the investigation, of reports of the results of preclinical tests conducted before use of the drug on human beings (2) upon the manufacturer or sponsor obtaining signed agreements from each investigator to whom he transmits the drug that patients to whom the drug will be administered will be under the personal supervision of such investigator or of other investigators responsible to him, and (3) upon the establishment and maintenance of records, and the making of reports, of data obtained as the result of such investigational use of such drugs. The House version also provided that the exemption was to be conditioned upon the manufacturer's requiring (1) that experts testing the drug on human beings first inform such patients or their representatives of the experimental nature of the drug and obtain their consent to its use, and (2) that such experts certify that such consent will be obtained.

The committee of conference substituted revised language for the provision of the House version relating to giving information to, and obtaining the consent of, the patients or his representative in connection with the administration of experimental drugs. The conference substitute requires the Secretary to issue regulations con-

ditioning the exemption upon the manufacturer's or sponsor's requiring clinical investigators to certify that where they administer experimental drugs to human beings they will inform them, or their representatives, that the drugs are being used for investigational purposes and obtain their consent, except where providing such information and obtaining such consent would not be feasible, or would, in the professional judgment of the investigator, be contrary to the best interests of those human beings to whom such drugs are being administered. The conference substitute makes clear that the conditions prescribed in the House version are not the sole conditions that may be imposed for the protection of the public health.

Both the Senate and House versions added to the new drug section (Sec. 505) of the Federal Food, Drug, and Cosmetic Act a new subsection (j) authorizing the Secretary by regulation or special order, to require manufacturers of previously cleared new drugs to keep records, and make reports to him, of information obtained by them as to experience with respect to such drugs. The conference substitute provides that the Secretary's regulations or orders under this new subsection, and regulations issued under Section 505(i) with respect to investigational drugs, must have due regard for the professional ethics of the medical profession and the interests of patients, and provides, where the Secretary deems it appropriate, for examination upon request, by persons to whom the regulations are applicable, of similar information received by the Secretary. This provision was in the bill as originally passed by the Senate.